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Early detection of acute renal failure by serum cystatin C

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Background. Acute renal failure (ARF) is associated with high mortality. Presently, no specific therapy for ARF exists. Therefore, early detection of ARF is critical to prevent its progression. However, serum creatinine, the standard marker to detect ARF, demonstrates major limitations. We prospectively evaluated whether serum cystatin C detected ARF earlier than serum creatinine.

Methods. In 85 patients at high risk to develop ARF, serum creatinine and cystatin C were determined daily. ARF was defined according to the Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and ESRD (RIFLE) classification when creatinine increased by ≥50% (R-criteria), by ≥100% (I-criteria), or by ≥200% (F-criteria). In analogy, ARF was detected when cystatin C increased by ≥50%, by ≥100%, or by ≥200%.

Results. Forty-four patients developed ARF and 41 served as controls. In ARF by R-, I-, and F-criteria, the increase of cystatin C significantly preceded that of creatinine. Specifically, serum cystatin C increased already by ≥50% 1.5 ± 0.6 days earlier compared to creatinine. Serum cystatin C demonstrated a high diagnostic value to detect ARF as indicated by area under the curve of the ROC analysis of 0.82 and 0.97 on the two days before the R-criteria was fulfilled by creatinine. Cystatin C detected ARF according to the R-criteria with a sensitivity of 55% and 82% on these days, respectively. Cystatin C also performed excellently, detecting ARF defined by the I- and F-criteria two days prior to creatinine, and moderately well predicting renal replacement therapy in the further course of ARF. Additionally, low T_3- or T_3/T_4 syndrome, glucocorticoid deficiency and excess did not affect cystatin C levels, adding to its usefulness in critically ill patients with ARF.

Conclusion. Serum cystatin C is a useful detection marker of ARF, and may detect ARF one to two days earlier than creatinine.

Acute renal failure (ARF) is common in hospitalized patients, with a mortality rate between 30% and 90% [1–6]. ARF markedly increases the mortality rate independently of other factors [3, 5, 7]. In the absence of effective, specific therapies for ARF, the early and accurate detection of ARF is crucial to prevent its progression, and thereby, to potentially improve its outcome [8–10]. In clinical practice, the detection of ARF, which is characterized by a rapid decline of the glomerular filtration rate (GFR), is based on an increase of serum creatinine [11]. However, there are major limitations to the use of creatinine for estimating glomerular filtration rate (GFR). Serum creatinine does not accurately reflect GFR during the nonsteady state of ARF by underestimating GFR [12]. Thus, minor changes of creatinine, as typically seen early in ARF, may already reflect substantial declines in GFR. Furthermore, serum creatinine inaccurately estimates GFR due to tubular secretion and reabsorption of creatinine, and nonrenal factors that may apply to ARF patients who are predominantly critically ill [12].

To overcome these obstacles, there is an extensive search for improved laboratory markers of impaired renal function [13, 14]. Cross-sectional studies in chronic renal insufficiency identified serum cystatin C as a promising, easily measurable marker to estimate GFR with a higher diagnostic value than serum creatinine [15, 16]. Cystatin C is a 13 kD endogenous cysteine proteinase inhibitor and is produced by nucleated cells at a constant rate. Cystatin C is freely filtered by the glomerulus, reabsorbed, and catabolized, but it is not secreted by the tubules [17, 18]. Further studies demonstrated the superiority of serum cystatin C compared to creatinine, especially to detect minor GFR reduction [19, 20]. This finding was confirmed by a recent meta-analysis [21]. Previous longitudinal studies on serum cystatin C predominantly suggested that serum cystatin C performed better than serum creatinine as a marker to detect acute changes of GFR [22–26]. However, these studies were limited because they examined either GFR changes in small patient samples or did not include controls [22, 23, 25, 26]. Furthermore limiting, most studies were conducted in renal transplant recipients early after transplantation [22–25], and high-dose glucocorticoid medication may have interfered with serum cystatin C [27, 28].

The purpose of this study was to prospectively evaluate serum cystatin C as a marker to detect ARF and to test

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whether cystatin C could detect ARF earlier than serum creatinine. In addition, we studied the effect of low T_3- or T_3/T_4 syndrome, glucocorticoid deficiency, and excess on serum cystatin C, because these conditions are frequent in critical illness, such as ARF, and may limit the diagnostic value of cystatin C.

METHODS

All patients in three surgical and medical intensive care units (ICU) at the University Hospital Essen with initially normal GFR, defined by a serum creatinine below 115 μmol/L measured at least twice consecutively, were screened for predisposing factors of ARF. Predisposing factors screened for were age above 70 years, cardiogenic or hemorrhagic shock, decompensated liver cirrhosis, chronic heart failure NYHA class IV, malignant lymphoma or acute leukemia, acute respiratory failure requiring mechanical ventilation, diabetes, valve surgery with aortocoronary bypass, and sepsis [29–31]. Patients with two or more predisposing factors were regarded as high-risk patients for ARF and were further evaluated. We excluded patients with aortic aneurysms, with hyper- or hypothyroidism, and patients receiving glucocorticoid or thyroid hormone therapy, because these conditions were demonstrated to be associated with increased or decreased serum cystatin C levels independent of renal function [27, 28, 32–34]. We also excluded patients expected to be possibly discharged from ICU within the next four days or to decease shortly, and those on renal replacement therapy within four days. No patient received cimetidine or trimethoprim. Eighty-five high-risk patients for ARF were included and prospectively studied.

From each patient serum samples were collected daily between 7 and 9 a.m. until discharge from ICU. Serum creatinine was determined on the day of sample collection and aliquots for serum cystatin C, total triidothyronine (T_3), total thyroxine (T_4), free thyroxine (fT_4), thyroid stimulating hormone (TSH), and cortisol measurements were stored at −20°C. Serum creatinine was measured by a modified Jaffe method with protein precipitation using an alkaline picrate reaction. Serum cystatin C was measured by immunonephelometric method (Dade Behring, Marburg, Germany) within two weeks after sample collection. Upper reference values were 114 μmol/L for serum creatinine and 1.01 mg/L for serum cystatin C, as previously described [16]. Previously, in our laboratory intra-assay and interassay imprecision averaged 3.0% and 4.4%, respectively. Accuracy, expressed as the difference between the expected and the measured values of cystatin C control material, was 2.8%. Clinical data were extracted from records of the hospital stay. ARF was detected according to the first three RIFLE (indicating the level of renal impairment: Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and ESRD) criteria of the GFR domain [35], which are (*1*) risk (R): an increase of serum creatinine ≥50% from baseline; (*2*) injury (I): an increase of serum creatinine ≥100% from baseline; and (*3*) failure (F): an increase of serum creatinine ≥200% from baseline. In analogy, ARF was detected when cystatin C increased by ≥50%, ≥100%, or ≥200% from baseline. In patients with ARF, serum creatinine and cystatin C were analyzed for the day the ARF risk criteria was fulfilled according to serum creatinine (R-day 0), and on the three days prior to R-day 0 (R-day −3 to −1). R-day –3 was termed baseline. The day the ARF injury- or failure-criteria was fulfilled according to serum creatinine was defined as I-day 0 or F-day 0. Serum creatinine and cystatin C were analyzed on the two days prior to I-day 0 or F-day 0, respectively (I-day −2 and −1, or R-day −2 and −1). Patients who did not develop ARF served as controls. In controls, serum creatinine and serum cystatin C were analyzed from the serum of five to six consecutive days starting from enrollment.

Serum T_3, T_4, fT_4, TSH, and cortisol were measured from samples of R-day −3. Low T_3- or T_3/T_4 syndrome was defined as decreased T_3, T_4, and fT_4 concentrations in the reference range, or decreased and decreased TSH values. Corticosteroid insufficiency and excess of critically ill were defined by serum cortisol concentrations <414 and >1406 nmol/L, respectively [36]. The latter cut-off value was derived from the 95th percentile of serum cortisol in ICU patients from several studies [37–43]. The study protocol was approved by the local institutional review board, and it is in accordance with the Helsinki Declaration of 1975 as revised in 1996. Informed consent was obtained from all patients prior to enrollment.

Statistical analysis

The primary end point was the day ARF was detected by serum creatinine according to the risk-criteria of the RIFLE classification, or the respective increase of serum cystatin C. Prior to the study, an analysis was performed to estimate the necessary patient number in each group required to detect a between-group difference of one SD or less, with a 90% power and an a error less than 0.05 [14]. Based on the biological variability of serum creatinine and serum cystatin C described in previous studies, a minimum of 35 patients was calculated for each group [25, 44, 45].

Secondary end points were the days ARF was detected by serum creatinine according to the injury- and failure-criteria, or the respective increases of serum cystatin C. Furthermore, we evaluated whether the etiology of ARF or urine volumes <0.5 mL/kg/hour for six hours (risk-criteria in the urine output domain of the RIFLE classification [35]) would affect the value of a ≥50% increase

Table 1. Characteristics of patients

	ARF	Control
N	44	41
Age *years*	70 ± 8	63 ± 11
Female/Male *N*	15/29	16/25
Primary diagnosis *N*		
Acute leukemia/lymphoma	3 (7%)	5 (12%)
Cardiovascular disease	19 (43%)	22 (53%)
Hepatic failure	7 (16%)	6 (15%)
Respiratory failure	5 (11%)	2 (5%)
Sepsis	7 (16%)	4 (10%)
Shock	2 (5%)	0 (0%)
Others	1 (2%)	2 (5%)
Etiology of ARF *N*		
Ischemia—prerenal	5 (11%)	n.a.
Nephrotoxic	4 (9%)	n.a.
Sepsis	8 (18%)	n.a.
Combination	27 (62%)	n.a.

ARF is acute renal failure. Values are partially expressed as mean ± SD.

Table 2. Risk-criteria of the RIFLE classification: Serum cystatin C and creatinine on the three days prior to (R-day –3 to R-day –1) and on the day ARF was detected by creatinine (R-day 0) in ARF patients and controls

	R-Day –3	R-Day –2	R-Day –1	R-Day 0
ARF				
Cystatin C *mg/L* (%)				
	0.81 ± 0.13	1.13 ± 0.26[b]	1.45 ± 0.32[b]	1.79 ± 0.36[b]
	100	142 ± 30[b]	182 ± 39[b]	226 ± 51[b]
Creatinine µ*mol/L* (%)				
	74 ± 12	80 ± 15	90 ± 11[a]	139 ± 18[a]
	100	107 ± 14	121 ± 12[a]	189 ± 34[a]
Control				
Cystatin C *mg/L* (%)				
	0.88 ± 0.19	0.93 ± 0.24	0.95 ± 0.32	0.96 ± 0.27
	100	106 ± 18	107 ± 19	109 ± 19
Creatinine µ*mol/L* (%)				
	80 ± 13	81 ± 16	80 ± 15	79 ± 17
	100	103 ± 14	102 ± 15	101 ± 18

ARF is acute renal failure. Values are expressed as mean ± SD. Percent of the values from R-day –3 are additionally presented.
[a] $P < 0.05$ by one-way ANOVA with Student-Newman–Keuls multiple comparison procedure.
[b] $P < 0.05$ by one-way ANOVA on ranks with Dunn's multiple comparison procedure.

of cystatin C to detect ARF. Finally, we studied the effect of low T_3- or T_3/T_4 syndrome, cortisol deficiency, and excess on the diagnostic value of cystatin C to detect ARF by cystatin C, and the value of cystatin C increased by ≥50% to predict renal replacement therapy (RRT) in the further course of ARF. Data are presented as mean and standard deviation unless otherwise indicated. Values are expressed either as absolute values or as percent of the values from R-day –3. After testing for normal distribution, continuous data were compared either with the Student *t* test or the Mann-Whitney rank-sum test, analysis of variance (ANOVA), or ANOVA on ranks, followed by the Student-Newman–Keuls or Dunn's multiple comparison procedure. Categorical data were compared by two-tailed Fisher exact or Chi-square test. $P < 0.05$ was considered to be statistically significant. Nonparametric receiver operating characteristics (ROC) curves of sensitivity and specificity with the respective areas under the curve (AUC) for cystatin C were generated. Sensitivity and specificity were calculated according to the definitions of the R-, I-, and F-criteria of ARF, with the respective cut-off values described above.

RESULTS

Of the 85 patients studied, 44 patients developed ARF according to the R-criteria, detected by an increase of serum creatinine ≥50%. In 41 patients (93%), ARF progressed to the I-criteria (increase of creatinine ≥100%) 1.2 ± 0.9 days after fulfilling the R-criteria. Furthermore, in 28 patients (64%), ARF progressed to the F-criteria (increase of creatinine ≥200%) 0.9 ± 0.4 days after reaching the I-criteria. In the further course of ARF, 17 patients (38%) required RRT. Acute renal failure was caused in the majority of patients by a combination of the etiologies ischemia, prerenal, nephrotoxicity, and sepsis. The other 41 patients without ARF served as controls. Patient characteristics did not differ between both groups, as demonstrated in Table 1.

Serum creatinine and cystatin C were within the reference ranges for controls as well as ARF patients three days before ARF was detected by an increased creatinine according to the R-criteria (R-day –3) (Table 2). The ARF patients and the controls did not statistically differ in respect to serum creatinine and cystatin C on R-day –3. In ARF, serum creatinine increased slightly on R-day –2 and R-day –1 (Table 2). Although this rise was statistically significant on R-day –1, it was markedly smaller than 50%, and the absolute creatinine values remained predominantly within the reference range. On R-day 0, serum creatinine had significantly increased, and by definition, the percent values had risen by ≥50% compared to R-day –3. In ARF, serum cystatin C and the respective percent values rose more rapidly compared to creatinine and had already increased significantly on R-day –2. The mean percent increase of cystatin C reached approximately 50% on R-day –2. On R-day –1 and R-day 0, a substantial further rise of serum cystatin C and its percent values was observed. Thus, serum cystatin C detected ARF 1.5 ± 0.6 days earlier than serum creatinine according to the R-criteria ($P < 0.001$). As demonstrated in Tables 3 and 4, percent values of serum cystatin C were also higher than serum creatinine two days prior to ARF detection by serum creatinine, according to the I- and F-criteria. Furthermore, serum cystatin C exhibited a faster rise in ARF patients than creatinine. The percent values reached the I- and F-criteria on I-day –1 and F-day –1, respectively (Tables 3 and 4). Serum cystatin C

Table 3. Injury-criteria of the RIFLE classification: Serum cystatin C and creatinine on the two days prior to (I-day –2 and I-day –1) and on the day ARF was detected by creatinine (I-day 0) in ARF patients and controls

	I-Day –2	I-Day –1	I-Day 0
ARF			
Cystatin C *mg/L* (%)			
	1.43 ± 0.42	1.74 ± 0.50[a]	2.17 ± 0.61[a]
	180 ± 47	219 ± 56[a]	272 ± 81[a]
Creatinine μ*mol/L* (%)			
	87 ± 24	119 ± 27[b]	167 ± 34[b]
	119 ± 21	167 ± 24[b]	245 ± 39[b]
Control			
Cystatin C *mg/L* (%)			
	0.92 ± 0.23	0.90 ± 0.20	0.92 ± 0.19
	108 ± 23	107 ± 24	109 ± 26
Creatinine μ*mol/L* (%)			
	83 ± 15	84 ± 17	80 ± 17
	102 ± 25	107 ± 22	102 ± 24

ARF is acute renal failure. Values are expressed as mean ± SD. Percent of the values from R-day –3 are additionally presented.
[a,b] $P < 0.05$ by one-way ANOVA on ranks with Dunn's multiple comparison procedure.

Table 4. Failure-criteria of the RIFLE classification: Serum cystatin C and creatinine on the two days prior to (F-day –2 and F-day –1) and on the day ARF was detected by creatinine (F-day 0) in ARF patients and controls

	F-Day –2	F-Day –1	F-Day 0
ARF			
Cystatin C *mg/L* (%)			
	1.90 ± 0.58	2.53 ± 0.55[b]	2.86 ± 0.75[b]
	244 ± 69	327 ± 70[b]	344 ± 92[b]
Creatinine μ*mol/L* (%)			
	101 ± 27	164 ± 31[a]	228 ± 32[a]
	147 ± 30	240 ± 37[a]	337 ± 24[a]
Control			
Cystatin C *mg/L* (%)			
	0.89 ± 0.21	0.88 ± 0.19	0.91 ± 0.22
	105 ± 24	104 ± 21	108 ± 28
Creatinine μ*mol/L* (%)			
	80 ± 16	82 ± 17	81 ± 15
	99 ± 28	106 ± 27	104 ± 23

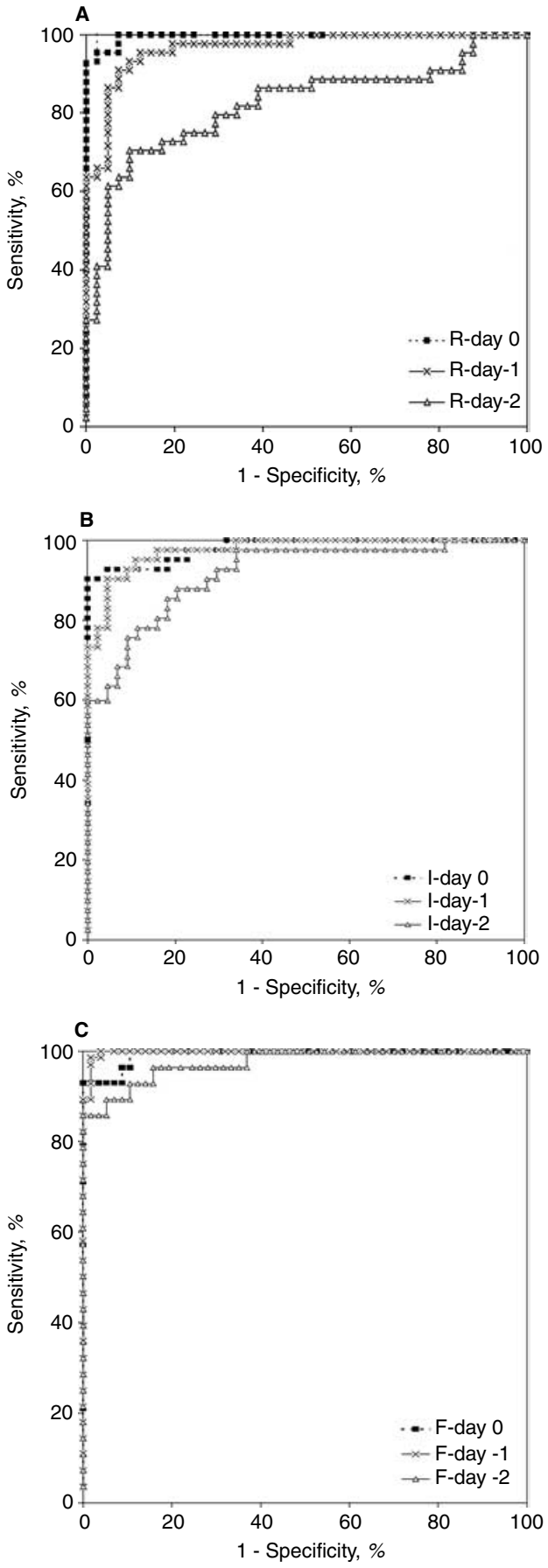
ARF is acute renal failure. Values are expressed as mean ± SD. Percent of the values from R-day –3 are additionally presented.
[a] $P < 0.05$ by one-way ANOVA with Student-Newman–Keuls multiple comparison procedure.
[b] $P < 0.05$ by one-way ANOVA on ranks with Dunn's multiple comparison procedure.

had increased by ≥100% 1.2 ± 0.9 days, and by ≥200% 1.0 ± 0.6 days prior to serum creatinine. Controls did not demonstrate any significant changes in serum creatinine or cystatin C during the entire study period (Tables 2 to 4).

The ROC curves, evaluating the value of serum cystatin C to detect ARF according to an increase ≥50%, showed that this marker performed overall well from R-day –2 to R-day 0. Areas under the curve were 0.82 [95% confidence interval (CI) 0.71–0.92] for R-day –2, 0.97 (95% CI 0.94–0.99) for R-day –1, and 0.99 (95% CI 0.98–1.00) for R-day 0 (Fig. 1A). Applying the cut-off value of an increase ≥50%, cystatin C had a moderate sensitivity and a good positive predictive value on R-day –2, which both improved considerably on R-day –1 and were excellent on R-day 0 (Table 5). As demonstrated by ROC curves, serum cystatin C had a good diagnostic performance to detect ARF by an increase ≥100% on I-day –2 with an AUC of 0.92 (95% CI 0.85–0.96). The diagnostic performance of cystatin C increased markedly with AUCs of 0.98 (95% CI 0.94–0.99) on I-day –1, and 0.98 (95% CI 0.95–0.99) on I-day 0 (Fig. 1B). Sensitivity of cystatin C to detect ARF by to an increase ≥100% was low on I-day –2, but increased substantially on I-day –1 and I-day 0 (Table 5). Positive predictive values were excellent for I-day –2 to I-day 0. Cystatin C performed excellently detecting ARF according to an increase ≥200% on F-day –2 with an AUC from the respective ROC plot of 0.97 (95% CI 0.93–0.99) (Fig. 1C). This further improved on F-day –1 and F-day 0 with AUCs of 0.99 (95% CI 0.99–1.00) and 0.99 (95% CI 0.98–1.00), respectively. In keeping with the results from ROC analysis, cystatin C showed low sensitivity to predict ARF according to an increase ≥200% on F-day –2 (Table 5). However, sensitivity increased on F-day –1 and F-day 0. Positive predictive values were excellent for F-day –2 and F-day –1, and moderate for F-day 0. Applying the cut-off of an increase ≥50%, ≥100%, and ≥200%, specificity approached 100% for cystatin C on all days studied.

Testing the predictive value of a serum cystatin C increase ≥50% for the requirement of RRT in the further course of ARF as another important end point provided a sensitivity of 53% (95% CI 31–74) and specificity of 82% (95% CI 70–89) on R-day –2, a sensitivity of 76% (95% CI 53–90) and specificity of 93% (95% CI 84–93) on R-day –1, and a sensitivity of 82% (95% CI 59–94) and specificity of 93% (95% CI 84–97) on R-day 0. Positive predictive value was low on R-day –2 [45% (95% CI 26–66)], and improved for R-day –1 and R-day 0 [76% (95% CI 53–90, and 78% (95% CI 55–91), respectively]. Negative predictive values for a serum cystatin C increase ≥50% to predict the requirement of RRT were good to excellent with 86% (95% CI 75–93) on R-day –2, 93% (95% CI 84–97) on R-day –1, and 95% (95% CI 86–98) on R-day 0. The value of a serum cystatin C increase ≥50% to predict the requirement of RRT was moderate to good with AUCs of the respective ROC plots of 0.69 (95% CI 0.51–0.84) for R-day –2, 0.75 (95% CI 0.62–0.85) for R-day –1, and 0.76 (95% CI 0.69–0.85) for R-day 0.

There was no significant association between the detection of ARF according to a rise of serum cystatin C by ≥50% and the etiologies of ARF ($P = 0.38$). In ARF patients, urine volume remained stable from R-day –3 (1.56 ± 0.48 mL/kg/hour) to R-day –1 (1.44 ± 0.65 mL/kg/hour). A moderate decrease of urine



volume was noticed on R-day 0 (1.23 ± 0.81 mL/kg/hour) ($P = 0.24$). Two ARF patients developed urine volumes <0.5 mL/kg/hour on R-day –1 another four ARF patients on R-day 0, thus also fulfilling the R-criteria of the urine output domain of the RIFLE classification [35]. In the other 38 ARF patients, urine volume on R-day 0 did not differ from R-day –3 (1.43 ± 0.66 mL/kg/hour). In the six patients with reduced urine volume, serum cystatin C detected ARF 1.5 ± 0.5 days prior to the decrease in urine volume. In controls, urine volumes remained stable and did not differ from those of ARF patients on R-day −3.

ARF and control patients did not markedly differ in respect to T_3, T_4, fT_4, TSH, and cortisol values (Table 6). Seventeen ARF patients (39%) presented with low T_3- or T_3/T_4 syndrome compared to 13 controls (32%) ($P = 0.65$). Ten ARF (23%) and nine control patients (20%) had serum cortisol <414 nmol/L ($P = 0.86$). Serum cortisol concentrations were >1304 nmol/L in 3 ARF (7%) and 4 control patients (10%) ($P = 0.71$). From R-day −2 to R-day 0, serum cystatin C was not significantly different in ARF and control patients with or without low T_3- or T_3/T_4 syndrome. Similarly, cystatin C values did not significantly differ either in ARF or control patients with serum cortisol < or ≥414 nmol/L, and ≤ or >1406 nmol/L on R-day −2 to R-day 0.

DISCUSSION

Our results indicate that serum cystatin C performs well as a marker to detect ARF. In addition, cystatin C may permit to detect the development of ARF one to two days earlier than serum creatinine, the current standard marker for ARF. We found that cystatin C detected ARF earlier according to a more sensitive (increase ≥50%) and to more specific definitions (increase ≥100% or ≥200%), which are analogous to the R-, I-, and F-criteria of the recently proposed RIFLE classification [35]. As a further major finding, a serum cystatin C increase ≥50% was demonstrated to predict the RRT requirement in the course of ARF moderately well. Thus, serum cystatin C may be a valid marker in the early and later stages of ARF. Our findings are of clinical importance because early detection of ARF can provide time to prevent the progression of ARF [8–10]. Early initiation of preventive measures may improve the outcome in ARF, a condition that substantially increases mortality [3, 5, 6, 7].

Fig. 1. ROC plots demonstrating the performance of serum cystatin C to detect ARF by an increase ≥50% (*A*), ≥100% (*B*), and ≥200% (*C*). The ROC curves of the two days prior to ARF and of the day ARF was detected by serum creatinine according to the R-, I-, and F-criteria, are presented: R-day −2 to R-day 0 (A), I-day −2 to I-day 0 (B), and F-day −2 to F-day 0 (C).

Table 5. Diagnostic performance of serum cystatin C detecting ARF by an increase ≥50%, ≥100%, and ≥200% two days and one day (day −2 and −1) prior and on the day (day 0) ARF was detected by serum creatinine according to the risk (R)-, injury (I)-, and failure (F)-criteria of RIFLE

	R-Day −2	R-Day −1	R-Day 0
Risk criteria			
ARF patients fulfilling criteria *N*	24	36	42
Sensitivity	55% (45–64)	82% (73–88)	98% (93–99)
Specificity	95% (89–98)	95% (89–98)	93% (86–97)
PPV	92% (76–98)	95% (83–99)	93% (82–98)
NPV	66% (53–77)	83% (70–91)	95% (84–99)
	I-Day −2	I-Day −1	I-Day 0
Injury criteria			
ARF patients fulfilling criteria *N*	16	31	38
Sensitivity	39% (29–49)	76% (66–84)	93% (85–97)
Specificity	100% (96–100)	100% (96–100)	96% (90–99)
PPV	100% (81–100)	100% (89–100)	95% (84–99)
NPV	63% (51–74)	81% (69–89)	93% (82–98)
	F-Day −2	F-Day −1	F-Day 0
Failure criteria			
ARF patients fulfilling criteria *N*	11	24	27
Sensitivity	40% (30–51)	85% (76–91)	96% (90–99)
Specificity	100% (96–100)	100% (96–100)	92% (84–96)
PPV	100% (74–100)	100% (86–100)	87% (71–95)
NPV	76% (65–84)	93% (83–97)	98% (90–100)

PPV, positive predictive value; NPV, negative predictive value. 95% CIs are given in parentheses.

Table 6. Serum concentrations of thyroid hormones, TSH, and cortisol in ARF and control patients three days prior to the detection of ARF by creatinine according to the risk-criteria

	Range	ARF	Control	*P* value
T_3 *nmol/L*	1.2–3.1	1.2 ± 0.6	1.3 ± 0.4	0.18[a]
T_4 *nmol/L*	58–154	74 ± 31	65 ± 32	0.19[b]
FT_4 *pmol/L*	10–25	18 ± 3	14 ± 3	0.17[b]
TSH *mU/L*	0.3–3.0	1.4 ± 1.2	1.9 ± 1.1	0.10[a]
Cortisol *nmol/L*	130–690	744 ± 317	714 ± 329	0.56[a]

ARF is acute renal failure. Values are expressed as mean ± SD.
[a]Testing was done using the Mann-Whitney rank-sum.
[b]Testing was done using Student *t* test.

Therefore, serum cystatin C could aid to advance the RIFLE classification after external validation of our results.

Cystatin C has been identified as a superior GFR marker to creatinine in chronic renal insufficiency with small variability [13, 15, 16, 19–22, 44, 45]. Serum cystatin C measurement is highly accurate and precise [15, 44, 46]. The commercially available immunonephelometric assay provides rapid, automated measurement of cystatin C and requires few minutes until results are available [16, 46]. Additionally, preanalytic factors such as routine clinical storage conditions, freezing and thawing cycles, or interfering substances, such as bilirubin or triglycerides, do not affect cystatin C measurement [44, 46].

The few published longitudinal studies on cystatin C predominantly support our finding that serum cystatin C reflects GFR changes more rapidly compared to serum creatinine [23, 25, 26]. One explanation may be that cystatin C, unlike creatinine, resembles more closely an ideal endogenous marker of glomerular filtration [17, 18], except for a few, negligible exceptions [27, 28, 32–34]. This is in contrast to the numerous nonrenal factors that influence the generation of creatinine, its tubular secretion, and backleak, which may result in inaccurate reflection of GFR by creatinine [12]. Another potential explanation emerges from recent observations that cystatin C and creatinine differ in regard to their glomerular filtration characteristics during pregnancy and diabetic nephropathy [47, 48]. It remains speculative whether this phenomenon occurs also in ARF, but alterations in glomerular pore size could cause differences in the glomerular filtration of cystatin C and creatinine during ARF. However, there are conflicting data, although of smaller patient populations, which demonstrate a more rapid rise of serum creatinine compared to cystatin C in acute renal graft rejection [22, 24].

Besides ARF, no other factor was identified to modify serum cystatin C levels, which enhances its usefulness as detection marker of ARF. Neither the etiology of ARF nor urine volume demonstrated any effect on the predictive value of serum cystatin C in ARF.

Low T_3- or T_3/T_4 syndrome, glucocorticoid deficiency, or excess did not markedly affect serum cystatin C, excluding these factors as nonrenal confounders of serum cystatin C in ARF. This is crucial because these endocrine disorders may frequently occur in critically ill ARF patients. However, serum cortisol levels vary widely in critically ill patients, and no upper reference value has been defined yet. Thus, we derive the cut-off value of >1406 nmol/L for serum cortisol from various studies to analyze the potential effect of glucocorticoid excess on serum cystatin C in ARF [37–43]. In addition, we realize

that the diagnosis of glucocorticoid deficiency in our study was based on one random morning measurement without performing a corticotropin stimulation test, a procedure that is not unchallenged [36, 38]. Due to exclusion of the respective patients, our results may not be valid for patients on thyroid or high-dose glucocorticoid therapy, patients with aortic aneurysms, hyper- or hypothyroidism. Glucocorticoids were demonstrated to increase the transcription of the cystatin C gene, and thyroid hormones appear to have an increasing effect on cystatin C [30, 32, 49]. In contrast, hypothyroidism and aortic aneurysms are associated with low serum cystatin C levels [32–34].

Focusing on patients with initially normal serum creatinine values limits this study. However, these patients especially may profit more from early detection of ARF because they are generally given less attention in regard to ARF and may develop ARF unnoticed compared to those with already increased creatinine values at baseline. Yet, our findings may not apply to patients with acute on chronic renal failure. Additionally, our cohort may not be entirely representative for ARF, and our findings may not be valid for patients who develop ARF together with the associated increase of GFR markers more rapidly. Furthermore, our study was performed at three ICUs of one hospital, which may have made it vulnerable to a center effect. These results certainly require independent validation on a larger patient size. Because we did not measure GFR, we cannot and did not intend to comment whether serum cystatin C or creatinine correlate more accurately with decreases of GFR in ARF. In spite of this limitation, estimates of GFR as serum creatinine and cystatin C are considered to be acceptable markers to detect ARF in clinical settings [3–6, 11–14, 35].

CONCLUSION

Our results suggest that serum cystatin C is a useful detection marker in ARF, and superior to serum creatinine. Cystatin C may detect ARF one to two days earlier than creatinine. Early detection may provide time to prevent the progression of ARF and improve its negative impact on outcome.

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